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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,470	11/14/2005	Moshe Szyf	FC 14647-80	5007

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EXAMINER	
SHIN, DANA H	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,470	SZYF ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-10,20-22,24,25 and 27-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-10,20-22,24,25 and 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on and September 12, 2007.

Currently, claims 1, 6-10, 22, 24-25, and 27-31 are under examination on the merits.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112

Claims 22, 24-25, and 27-31 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons of record as set forth in the Office action mailed on June 13, 2007 and for the reasons stated below.

Applicant's arguments filed on September 12, 2007 have been fully considered but they are not persuasive. Applicant asserts that Example 1 in the specification shows *in vivo* inhibition of the instantly claimed antisense oligonucleotide comprising SEQ ID NO:10. Contrary to

applicant's assertions, Example 1 in the instant specification (pages 42-43) is exclusively directed to *in vitro* cell culture data wherein various carcinoma cell lines are transfected with antisense oligonucleotides complexed with Lipofectin, and it is found that there is no *in vivo* embodiment in Example 1. Furthermore, as evidently presented in applicant's own *in vitro* antisense transfection experimentation comprising five different antisense oligonucleotides, not all antisense oligonucleotides exert the same degree of target gene inhibition, and therefore it would have been unpredictable at the time of the invention whether the antisense oligonucleotide comprising SEQ ID NO:10 would have inhibited MBD2 gene in a mammal *in vivo* with a resultant cancer treatment effect as claimed. See Figure 4 that demonstrates varying degrees of target gene inhibition in cells *in vitro*. Accordingly, it is concluded that *in vivo* use of the claimed antisense oligonucleotide of SEQ ID NO:10 was not enabled and therefore would have necessitated undue experimentation at the time of the invention.

Claim Rejections - 35 USC § 102

Claim 1 remains rejected under 35 U.S.C. 102(b) as being anticipated by Zannis et al. (US 5,877,009) for the reasons of record as set forth in the Office action mailed on June 13, 2007 and for the reasons stated below.

Applicant's arguments filed on September 12, 2007 have been fully considered but they are not persuasive. Applicant argues the amended claim language obviates this rejection.

Contrary to applicant's assertions, claim 1 currently recites: "**an** antisense oligonucleotide and/or a siRNA molecule, or an analogue thereof, comprising **a** nucleotide sequence complementary to a mammalian MBD2/demethylase mRNA as set forth in SEQ ID

NO:10". With regard to the term "antisense oligonucleotide", applicant broadly defines it to mean an oligonucleotide having a nucleotide sequence that is complementary to a portion of the mRNA transcribed from the gene of interest." without further defining the structure (length limitation) of the claimed subject matter. See page 15. The specification, however, states that "there is provided an oligonucleotide inhibitor, or an analogue thereof, comprising from about 7 to about 100 nucleotides complementary to a mammalian MBD2/demethylase mRNA" or "comprising at least 7 consecutive nucleotides" from SEQ ID NO:10. See pages 2-3, 9, and 19.

Taken together, given the broadest reasonable interpretation of the claims consistent with the specification, the claimed oligonucleotide inhibitor still embraces an antisense oligonucleotide comprising at least 7 consecutive nucleotides of SEQ ID NO:10, wherein the inhibitor inhibits expression of a mammalian MBD2/demethylase gene.

Since the oligonucleotide of Zannis et al. comprising SEQ ID NO:66 meets the structural requirement set forth in the claims, the isolated oligonucleotide sequence of Zannis et al. will inherently inhibit expression of a mammalian MBD2/demethylase gene, since applicant did not provide evidence to the contrary.

Claim 1 remains rejected under 35 U.S.C. 102(e) as being anticipated by Wohlgemuth et al. (US 6,905,827 B2) for the reasons of record as set forth in the Office action mailed on June 13, 2007 and for the reasons stated below.

Applicant's arguments filed on September 12, 2007 have been fully considered but they are not persuasive. Applicant argues the amended claim language obviates this rejection.

For the same reasons stated above for maintaining the 102(b) rejection, this rejection is maintained. In summary, Wohlgemuth et al. teach a 50-mer oligonucleotide comprising SEQ DI NO:8110, which meets the structural requirement set forth in the claims, and therefore the isolated oligonucleotide sequence of Wohlgemuth et al. will inherently inhibit expression of a mammalian MBD2/demethylase gene.

New Objections/Rejections Necessitated by Amendments

Claim Objections

Claims 1, 22, and 25 are objected to for containing non-elected subject matter: siRNA molecule. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 6-10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation

such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claim is drawn to an antisense oligonucleotide comprising a nucleotide sequence complementary to MBD2 mRNA as set forth in SEQ ID NO:10.

Currently, SEQ ID NO:10 comprises "CACTCTCCCCCTCCCCCT", which, according to the claim language, should be complementary to the MBD2 mRNA sequence. The instant specification teaches that the oligonucleotide inhibitor of the present invention is targeted to SEQ ID NO:1 or 3 or 15. See page 9. With regard to the actual design of the antisense DNA oligonucleotide comprising the entire 18 nucleotides of SEQ ID NO:10, the specification states that it is designed to "hybridize to human MBD2 cDNA" that is "described in Hendrich, B., and Bird, A. (1998) *Mol Cell Biol* 18, 6538-6547)". See page 41. In addition, Figure 3 suggests that SEQ ID NO:10 is complementary to the 5' region of the MBD2 mRNA sequence.

Contrary to the disclosure of the specification, the instantly claimed SEQ ID NO:10 is not found to be complementary to any of the disclosed SEQ ID NOs:1, 3, and 13, nor is it found to hybridize to any of the human MBD2 cDNA sequences described in the Hendrich et al.

reference. See page 6540 of the Hendrich et al. reference, which expressly teaches that all MBD2 related sequences are "available in Genbank under accession nos. AF072240 to AF072252". If applicant's description of the antisense oligonucleotide comprising SEQ ID NO:10 disclosed on page 41 is correct, the complementary sequence of SEQ ID NO:10 must be located in one of the GenBank Accession Nos taught by Hendrich et al. However, contrary to applicant's statement, none of the GenBank Accession Nos contains the complementary sequence (sense sequence) of SEQ ID NO:10. Furthermore, the sequence search of SEQ ID NO:10 performed in various sequence databases, did not return the target gene "MBD2" as the nucleotide sequence that contains the complementary sequence of SEQ ID NO:10.

Since the identity of SEQ ID NO:10 differs from applicant's alleged statement that it hybridizes to the human MBD2 cDNA sequence of Hendrich et al., it is concluded that one of ordinary skill in the art would not have been able to make the instantly claimed antisense oligonucleotide comprising SEQ ID NO:10 based on the art-accepted human MBD2 cDNA sequence, and furthermore, the skilled artisan would not have been able to treat cancer comprising administering the antisense oligonucleotide of SEQ ID NO:10 by inhibiting MBD2 expression without undue experimentation, because the skilled artisan would have recognized that SEQ ID NO:10 does not hybridize to any of the fragments or variants of the known human MBD2 sequence and therefore would have foreseen unpredictable results both *in vitro* and *in vivo*.

Even though Example 1 describes that SEQ ID NO:10 reduces MBD2 mRNA expression level in cells *in vitro*, based on the content of the disclosure and the discrepancy between applicant's guidance/direction as to how to make the antisense oligonucleotide of SEQ ID NO:10

and the actual application of the directions provided by Hendrich et al. (i.e., instant SEQ ID NO:10 is not complementary to any of the known MBD2 sequence), undue amount of experimentation would have been required to make an antisense oligonucleotide, let alone a pharmaceutical composition, comprising the claimed SEQ ID NO:10.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
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